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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,632	CROMLISH ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-15,19 and 22-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-15,19 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Reissue Application

Claims 1-7, 9-15, 19, 22-27 are currently pending in this re-issue application.

Applicants' amendments and arguments filed on 1-25-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. However, new rejections/objections are now in place.

Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,543,297 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

Response to Amendment

The amendment to the claims filed on 1-25-05 is objected because it does not comply with the requirements of 37 CFR 1.173(b). All claims being currently amended in the amendment paper must comply with 37 CFR 1.173(b) which states that,

(b) *Making amendments in a reissue application.* An amendment in a reissue application is made either by physically incorporating the changes into the specification when the application is filed, or by a separate amendment paper. If amendment is made by incorporation, markings pursuant to paragraph (d) of this section must be used. If amendment is made by an amendment paper, the paper must direct that specified changes be made.

(1) Specification other than the claims . Changes to the specification, other than to the claims, must be made by submission of the entire text of an added or rewritten paragraph, including markings pursuant to paragraph (d) of this section, except that an entire paragraph may be deleted by a statement deleting the paragraph without presentation of the text of the paragraph. The precise point in the specification must be identified where any added or rewritten paragraph is located. This paragraph applies whether the amendment is submitted on paper or compact disc (see §§ 1.52(e)(1) and 1.821(c), but not for discs submitted under § 1.821(e)).

(2) ***Claims*** . An amendment paper must include the entire text of each claim being changed by such amendment paper and of each claim being added by such amendment paper. For any claim changed by the amendment paper, a parenthetical expression "amended," "twice amended," etc., should follow the claim number. Each changed patent claim and each added claim must include markings pursuant to paragraph (d) of this section, except that a patent claim or added claim should be canceled by a statement canceling the claim without presentation of the text of the claim.

(3) Drawings. One or more patent drawings shall be amended in the following manner: Any changes to a patent drawing must be submitted as a replacement sheet of drawings which shall be an attachment to the amendment document. Any replacement sheet of drawings must be in compliance with § 1.84 and shall include all of the figures appearing on the original version of the sheet, even if only one figure is amended. Amended figures must be identified as "Amended," and any added figure must be identified as "New." In the event that a figure is canceled, the figure must be surrounded by brackets and identified as "Canceled." All changes to the drawing(s) shall be explained, in detail, beginning on a separate sheet accompanying the papers including the amendment to the drawings.

(i) A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be included. The marked-up copy must be clearly labeled as "Annotated Marked-up Drawings" and must be presented in the amendment or remarks section that explains the change to the drawings.

(ii) A marked-up copy of any amended drawing figure, including annotations indicating the changes made, must be provided when required by the examiner.

(c) **Status of claims and support for claim changes** . Whenever there is an amendment to the claims pursuant to paragraph (b) of this section, there must

> also be supplied, on pages separate from the pages containing the changes, the status (i.e., pending or canceled), as of the date of the amendment, of all patent claims and of all added claims, and an explanation of the support in the disclosure of the patent for the changes made to the claims.
> (d) Changes shown by markings . Any changes relative to the patent being reissued which are made to the specification, including the claims, upon filing, or by an amendment paper in the reissue application, must include the following markings:
> (1) The matter to be omitted by reissue must be enclosed in brackets; and
> (2) The matter to be added by reissue must be underlined, except for amendments submitted on compact discs (§§ 1.96 and 1.821(c)). Matter added by reissue on compact discs must be preceded with "<U>" and end with "</U>" to properly identify the material being added.
> (e) Numbering of patent claims preserved. Patent claims may not be renumbered. The numbering of any claim added in the reissue application must follow the number of the highest numbered patent claim.

The amendment to the claims filed on 1-25-05 does not comply because applicants have filed a "claim listing" and a "marked up copy" which is no longer required. Applicants need to submit only a single listing of claims which shows all the changes made according to 1.173(b) above.

Defective Oath/Declaration

The reissue oath/declaration filed with the amendment filed on 1-25-05 is defective (see 37 CFR 1.175 and MPEP j 1414) because of the following;

1) Applicant fails to provide the residential address/mailing address of each and every inventor.

Claims 1-7, 9-15, 19, 22-27 are rejected as being based upon a defective reissue Declaration under 35 U.S.C. 251 as set forth above. See 37 CFR 1.175.

The nature of the defects in the Declaration is set forth in the discussion above in this Office action. Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants do not provide specific SEQ ID NO to the sequences depicted in the drawings either on the drawings or in the figure description. Please see particularly 37 CFR 1.821(d) and (e).

Applicant's request for transfer of electronic form of sequence information from the parent application to the instant application has been received and said transfer has been made.

Submission of the Original Patent

In response to the previous Office action, applicant has requested that this issue be held in abeyance until allowable subject matter is defined. However, the submission of original patent is no longer a requirement.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-7, 11, 14, and claims 4-5, 12-13, 15 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-3, 6-7, 11 and 14 are drawn to an assay for determining the COX-2 activity "of a sample" comprising the steps of adding a cell preparation (which is actually the source of the COX enzyme), a

sample comprising a COX-2 inhibitor and arachidonic acid followed by measuring the amount of PGE produced. The step (a) is highly confusing to the Examiner because it is not clear whether the "sample" in the preamble of the claims and the "sample" in step (2) of (a) are one and the same. If they are one and the same, then it is not clear to the Examiner as to how one of ordinary skill in the art can expect to test the activity of the sample having an inhibitor of the enzyme. It is not clear whether applicants meant to claim an assay to determine the "COX-2 *inhibitory* activity of a sample", wherein said sample comprises a putative COX-2 inhibitor. On the other hand if applicant did not mean the above, Examiner requests clarification.

Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

In response to the above rejection, applicant has traversed the above rejection arguing that claims are correct as they stand. Applicant submits that the sample mentioned in the preamble is the same as the "sample" mentioned subsequently and that those of skill in the art fully appreciate that the "putative COX-2 inhibitors" of the claims in question may be a potent inhibitor of COX-2 or a poor inhibitor of COX-2 or may be somewhere in between. Applicant continues the argument that COX-2 activity measured in the "sample" may be indistinguishable from zero (in the case of a potent COX-2 inhibitor), may be indistinguishable from a cell preparation having no putative inhibitor (in the case of a poor COX-2 inhibitor), or may be somewhere in between. Stated another way, the inhibitory activity is not something directly measured but it is something arrived at by calculating the difference in activity in samples with and without a putative inhibitor. While that may all be so, still the way applicant has written the claim leads to the confusion with respect to the source of the enzyme for the assay. As is, the

claim suggests that the source of the enzyme is the sample and one is measuring the COX-2 activity in said sample. However, upon closer examination of the assay, it becomes clear that the "sample" is not the source of the enzyme and that it is the osteosarcoma cell preparation that is the source of the enzyme and said "sample" indeed is the source for the inhibitor. Therefore as suggested by the Examiner in the previous Office action and in the instant Office action, applicant is urged to review the claim language. Perhaps, applicant meant to recite "An assay for determining the COX-2 *inhibitory* activity of a sample". The "sample" is the one comprising the putative COX-2 inhibitor and it is that inhibitor that is being assayed for its potential to inhibit COX-2. Either way, Examiner urges applicant to clarify the issue of COX-2 enzyme source for the assay, as to whether the enzyme comes from the "sample" or from the osteosarcoma cell preparation.

Claim 19, and claims 26 and 27 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19(b) refers to sequences in figures and recites specific SEQ ID NO in parentheses. Such a depiction is confusing and unclear to the Examiner. This is because applicants do not provide a SEQ ID NO for the sequences depicted in the figure and therefore it cannot be taken for granted that the sequences in the figures and those listed in the sequence listing with appropriate SEQ ID NO are one and the same. Examiner urges applicants to refrain from referring sequences to the figure and provide only SEQ ID NO. Correction is required.

Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

In response to the above rejection in the previous Office action, applicant has indeed amended claim 19 by deleting the brackets. However, the amendment has been made partially. Claim 19(b) continues to recite the SEQ ID NO in brackets. Examiner requests the applicant to amend the claim fully.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 9-10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rodan et al. (J. Bone Mineral Res. 1986, Vol. 1(2):213-220 cited in Form 1449). Claim 9-10 in this instant application is drawn to a composition comprising an osteosarcoma cell preparation having 8 $x10^4$ to $2x10^6$ cells per c.c. or 100-400 microgram of osteosarcoma microsomes and 10 to 20 micro liters of arachidonic acid per c.c. of cell preparation.

Rodan et al. teach several types of human osteosarcoma cell and provide cell culture composition of the same. The reference also teaches the use of said cells for assay of COX activity along with exogenous use of arachidonic acid in such reactions. Rodan et al. actually investigate the basis for differences in prostaglandin synthesis among osteosarcoma cell lines and examine the effect of a number of bone resorbing agents on prostaglandin production and report

that the differences in PGE synthesis between osteoblastic and non-osteoblastic rat osteosarcoma cells were associated with COX dependent release of arachidonic acid.

With the above teaching of Rodan et al. in hand, it would have been obvious to those skilled in the art to make several types of cell preparations to study the above aspects, one of which would be a cell preparation between 10^3 or 10^5 or 10^9 or 8 x10^4 to 2x10^6 osteosarcoma cells per c.c. or 100-400 microgram of osteosarcoma microsomes per c.c. of cell preparation (as required) along with varying amounts of arachidonic acid such as 10 to 20 or 100 micro liters. One of ordinary skill in the art would have been motivated to do so in order to set up reactions to study the effects of bone resorbing agents on PGE synthesis. One of ordinary skill in the art would have a reasonable expectation of success since Rodan et al. provide the cells and a detailed information regarding their role and their physiology.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-1600 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao
Primary Examiner
Art Unit 1652

February 21, 2005